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Case Report

A Boy Safely Treated with Tyrosine Kinase Inhibitors for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia with Osteolysis

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A three-year-old boy with Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukemia (Ph+ALL) presented with an osteolytic lesion in his right upper arm. Tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib are an essential component throughout the course of treatment for Ph+ALL. However, TKIs are reported to affect the bone metabolism. In the treatment course of the current patient, the osteolytic lesion quickly improved despite the continuous use of TKIs, even during the concomitant use of corticosteroids. This suggests that TKIs can be safely given with concomitant corticosteroids to children with Ph+ALL, even when osteolytic lesions are present.

Key words: acute lymphoblastic leukemia, children, tyrosine kinase inhibitor, osteolysis

Acute lymphoblastic leukemia (ALL) in children can present with symptoms attributed to bone lesions, such as bone pain [1]. While bone lesions and their symptoms usually resolve according to the treatment course, several drugs, including tyrosine kinase inhibitors (TKIs), can change the bone metabolism and cause adverse musculoskeletal effects [2-4], complicating the clinical course of children with bone lesions. Here, we report the case and clinical course of a 3-year-old Japanese boy with Philadelphia chromosome-positive B-cell precursor ALL (Ph+ ALL) who presented with an osteolytic lesion. Parental consent was obtained for this case report.

Case Presentation

A 3-year-old boy presented to a local hospital complaining of pain in the right upper arm and bilateral lower legs. Physical examination revealed no redness, swelling, or heat in the painful areas. There was no evidence of lymphadenopathy or hepatomegaly, but the spleen was palpable 1 cm below the costal margin. The white blood cell count in the peripheral blood was 9.27×10^9/L with no increase in blasts. X-ray imaging revealed osteolysis of the right humerus (Fig. 1A). Bone mineral markers were within normal range at presentation, with a corrected serum calcium concentration of 10.6 mg/dL, a phosphorus level of 6.9 mg/dL, and an alkaline phosphatase level of 327 U/L (using methods of the Japan Society of Clinical Chemistry).

A biopsy of the right humerus revealed leukemic cell infiltration. ALL was suspected, and the patient was referred to our university hospital for detailed diagnosis and treatment. Microscopic morphological examination revealed 55.6% lymphoblasts in the bone marrow.

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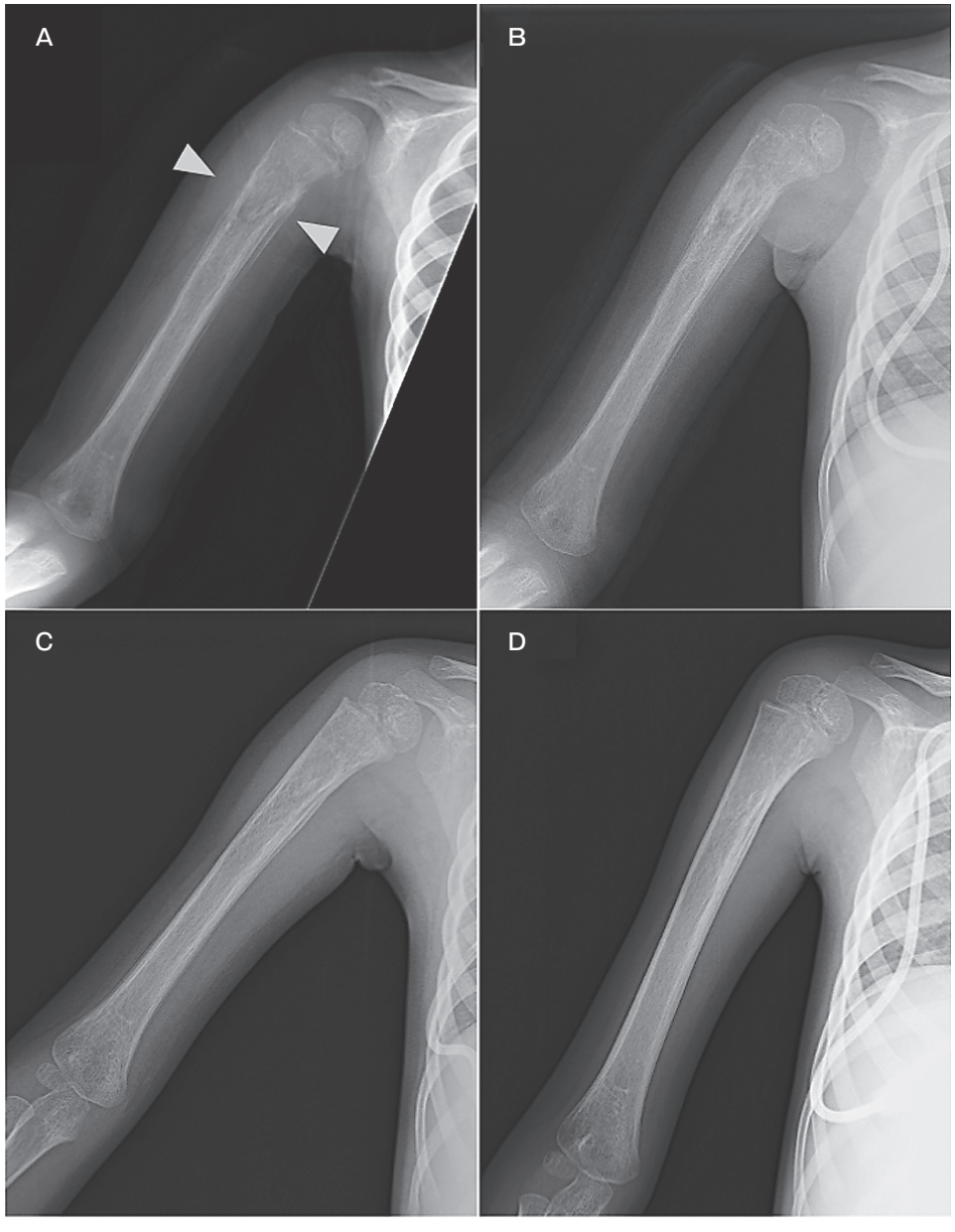

Fig. 1 Changes in the osteolytic lesion in the right arm of the patient. X-ray taken (**A**) before the start of chemotherapy and a tyrosine kinase inhibitor; (**B**) after an induction course, 1 month after (**A**); (**C**) after an early intensification course, 3 months after (**A**); and (**D**) after a total of four courses of intensification, 7 months after (**A**).

Flow cytometry of the bone marrow cells identified blast cells positive for HLA-DR, CD19, CD34, cytoplasmic-CD79a, and cytoplasmic-TdT. Karyotyping revealed [46, XY, t(9; 22) (q34; q11. 2)], and minor *BCR-ABL1* mRNA was detected. Based on these findings, the patient was diagnosed with Philadelphia chromosome-positive (Ph+) ALL.

We treated the patient with multiagent chemotherapy with imatinib, following the EsPhALL protocol [2] and the Japanese Pediatric Leukemia/Lymphoma Study Group Ph-13 protocol. Imatinib was started at 270 mg/m^2 from Day 15 of the induction phase, and morphological remission was achieved on Day 38 according to bone marrow examination. X-rays taken on Day 33 of the

induction phase showed bone formation (Fig. 1B, one month after diagnosis). Imatinib was increased to 340 mg/m^2 after the induction phase. Because the patient's *BCR-ABL1* transcript levels remained positive during the early intensification phase, imatinib was changed to dasatinib 60 mg/m^2 on Day 16 of the early intensification phase. On Day 50 of early intensification therapy, the patient's *BCR-ABL1* transcript levels became negative, and molecular remission was achieved. The osteolytic lesion had improved during treatment, as shown on X-rays taken at the end of the early intensification phase, 3 months after diagnosis (Fig. 1C), and after three high-risk blocks and one additional intensification course, 7 months after diagnosis (Fig. 1D). There was no recurrence of the osteolysis. Throughout the treatment course, we monitored serum calcium, phosphorus, and alkaline phosphatase, none of which showed abnormal values at any time. As the X-ray findings had continued to improve, it was deemed unnecessary to correct electrolyte imbalances or utilize bisphosphonates or denosumab. Dasatinib was continued until shortly before bone marrow transplantation, resumed on Day 40 after transplantation, and continued until eight months after transplantation, when it was discontinued. One year and five months after transplantation, *BCR-ABL1* became positive again, which was considered a relapse, and dasatinib was restarted at the same dose. Three months after relapse, the patient received chimeric antigen receptor T-cell therapy and has remained in remission for two years and two months at the time of writing. The patient continues taking dasatinib.

Discussion

ALL is the most common form of leukemia in children and accounts for approximately 30 percent of all pediatric neoplasms. Pediatric ALL is diagnosed with a wide range of symptoms, including musculoskeletal symptoms such as limb pain (43%) and bone pain (26%) [1]. Although the Philadelphia chromosome is present in 3-5% of children with ALL and has been associated with a poor prognosis, the prognosis of Ph+ ALL has greatly improved with the development of TKIs. Meanwhile, various systemic effects of TKIs have been reported, including cytopenia, infection, gastric toxicity, and osteonecrosis [2]. Additionally, several reports suggest that the use of TKIs affects the bone metabolism, where off-target effects of TKIs lead to decreased synthesis of osteoclasts, possibly decreased overall bone turnover, and alterations in the calcium and phosphate metabolism [4-6]. Moreover, in the previous literature, imatinib has been reported to reduce the number and activity of osteoclasts by inhibiting c-fms and c-kit signaling [6]. Imatinib has also been reported to inhibit platelet-derived growth factor signaling in osteoblasts, which reduces the number of osteoblasts but increases their activity [6]. Meanwhile, dasatinib has been reported to inhibit c-fms signaling and to induce mesenchymal stem cells to differentiate more into adipocytes rather than osteoblasts [7]. However, as these findings have almost always been based on the findings of adult patients with chronic myeloid leukemia, and as children have a much more rapid bone turnover than adults, there is evidence that TKIs can negatively affect bone formation during childhood. Several case reports of children treated with imatinib identified bone absorption findings or decreased bone formation, in contrast to adult cases, which usually show increased bone mineral density [8-10]. This could be more problematic in cases of osteolytic lesions or pathological fractures because their improvement could be delayed during the administration of TKIs. Furthermore, as treatment protocols for ALL also use corticosteroids, there is the additional concern that the combination of corticosteroids and TKIs might even more profoundly affect bone formation in the treatment of Ph+ ALL, although a study with a mouse model found that the incidence of osteonecrosis was not increased in the dexamethasone plus dasatinib group compared to the dexamethasone alone group [3].

Contrary to our concerns, the present patient's osteolytic lesion quickly improved despite the continuous use of imatinib or dasatinib, even during the concomitant use of corticosteroids. This implies that accelerated bone formation due to the improvement of leukemic infiltration by multiagent chemotherapy with a TKI could outweigh the possible negative effects of TKIs. In the present case, we did not measure detailed markers of bone metabolism, such as parathyroid hormone or 25-hydroxyvitamin D, which could be altered by TKIs. Further study including these markers would be warranted. Nevertheless, this case suggests that TKIs can be safely given to children with Ph+ ALL with concomitant corticosteroids, even when osteolytic lesions are detected.

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